Correlation of invasive Doppler flow wire with renal duplex ultrasonography in the evaluation of renal artery stenosis: The Renal Artery Stenosis Invasive Doppler (RAIDER) study

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Objective: **Determining renal resistive index (RI) in the setting of renal artery stenosis may predict which patients benefit from revascularization. Renal duplex ultrasonography (RDUS) is the traditional method of assessing RI, but it is not available in most invasive endovascular laboratories. Conversely, endovascular techniques to assess RI are available but not well validated. The primary goal was to determine if an invasive approach using an endovascular Doppler flow wire correlates with RI assessment using traditional noninvasive RDUS.**

Methods: **In a single-center prospective trial, patients were enrolled if they had known or suspected renovascular disease. A Doppler flow wire was placed in multiple segments of the renal artery, and peak (PSV) and end-diastolic velocities (EDV) were measured. RI was calculated using the formula: RI = [1 – (EDV/PSV)] × 100. Similarly, RI was also derived using standard RDUS. All patients underwent both RI techniques before any revascularization procedure. Secondary end points included assessing the correlation for pole-to-pole renal length assessment and PSV and EDV velocities using both invasive and noninvasive techniques. Pearson correlation coefficient calculations were used to determine degree of correlation.**

Results: **The study enrolled 20 patients, and 35 renal arteries were studied. Overall, Pearson correlation coefficient for invasive vs noninvasive RI assessment was 0.86 (95% confidence interval [CI], 0.73 to 0.93). The r values were 0.43 (95% CI, 0.11 to 0.67) for pole-to-pole renal length, 0.66 (95% CI, 0.54 to 0.76) for PSV, and 0.61 (95% CI, 0.48 to 0.72) for EDV determination. No major complications occurred during this study. Average time to perform invasive Doppler assessment was 10.4 ± 7.4 minutes per artery.**

Conclusions: **Invasive RI assessment using an endovascular flow wire technique correlates well with traditional noninvasive RDUS. A moderate statistical correlation also exists for pole-to-pole renal length, PSV, and EDV determinations. The procedure is safe and can be performed rapidly. (J Vasc Surg 2007;45:284-8.)**

Renal artery stenosis (RAS) is a complex clinical entity leading to a variety of clinical presentations, ranging from asymptomatic to combinations of hypertension, renal insufficiency, and volume disturbance syndromes such as flash pulmonary edema. RAS has been identified as an important and often reversible cause of secondary hypertension or renal failure, or both.[1,2]

Many clinicians presently use screening renal angiography as an adjunct to coronary or peripheral angiography. This practice often leads to renal artery revascularization based on degree of stenosis alone, irrespective of the clinical context. Although there is no clear consensus about the degree of renal artery narrowing that justifies revascularization, interventionalists generally define the minimal threshold for an angiographically significant artery stenosis to be a ≥50% luminal diameter reduction.[3,4] Even this is acknowledged as only an approximate guide to the hemodynamic effect of the stenosis.

Renal resistive index (RI) is a dimensionless index that assesses the degree of renal microvascular disease. Existing data suggest the RI is an important predictor of clinical benefit after renal revascularization and is considered a key element of RAS evaluation before invasive treatment.[5,6] The current standard technique used to derive the RI is noninvasive renal duplex ultrasonography (RDUS). Unfortunately, this test is not immediately available in most busy endovascular laboratories. The primary goal of the Renal Artery Stenosis Invasive Doppler (RAIDER) study is to correlate invasive measurements of RI using endovascular Doppler flow wire techniques with noninvasive, RDUS-derived measurements.

MATERIALS AND METHODS

Patient selection. Approval for this study was obtained from the Institutional Review Board of the participating hospital. Patients were enrolled after giving informed consent if they met study inclusion criteria. Included were patients referred for coronary or peripheral angiography who had suspected (hypertension resistant to

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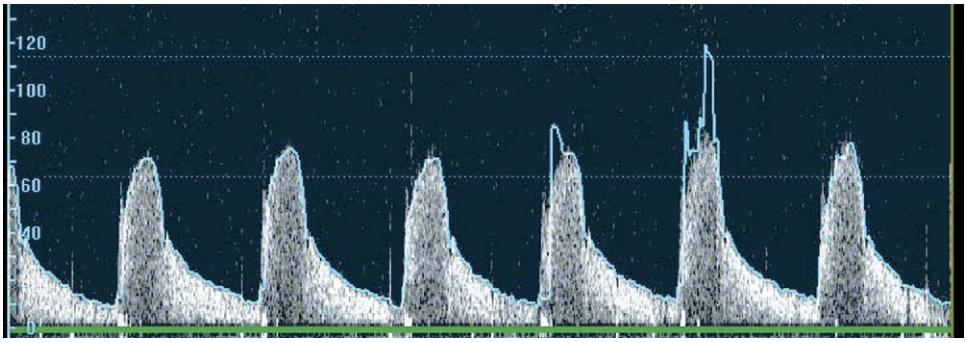

Fig 1. Example of invasive Doppler flow wire velocity waveforms in the mid renal artery. Peak systolic velocity here is 80 cm/s. End-diastolic velocity is 15 cm/s. This yields an RI of 81.

3 or more drugs including diuretic) or known renovascular disease. RAS was identified as arterial diameter narrowing ≥50% on angiography by visual estimate. Exclusion criteria included acute ST-segment elevation myocardial infarction, cardiogenic shock, or total occlusion of the renal artery precluding the use of a translesional guidewire, or other clinical or anatomic criteria that were considered too high-risk as determined by the senior physician operator. Pregnant women were also excluded. Only patients who underwent both invasive Doppler flow wire and RDUS assessments before any renal revascularization were included in the final analysis.

Renal angiography. Selective renal angiography was performed on all visualized renal arteries with an appropriately selected diagnostic catheter and hand injection of contrast. Angiography was performed with digital subtraction techniques when available. Quantitative angiography, stenosis assessment, and contrast-enhanced pole-to-pole renal length measurements were also performed. Specifically, stenosis severity was based on smallest vessel diameter using electronic calipers divided by the largest diameter in a normal-appearing segment of the main renal artery.

Invasive Doppler measurements. Doppler measurements were performed using a 0.014-inch Doppler-tipped Flowire (Volcano Therapuetics, Rancho Cordova, Calif) with concurrent heparin administration to maintain adequate anticoagulation. The device was advanced into the renal artery through the diagnostic catheter. The external tip of the Doppler wire was connected to a ComboMap pressure and flow system (Volcano Therapeutics). Doppler spectral forms were optimized by slowly rotating the J-shaped wire and monitoring both the image screen and the auditory Doppler signal (Fig 1).

Peak systolic velocities (PSV, cm/s) and end-diastolic velocities (EDV, cm/s) were recorded in the proximal, middle, and distal renal artery and also at a first-order segmental branch. RI values were calculated using the equation: $RI = [1 - (EDV/PSV)] \times 100$. The reported RI was an average of two to four measurements obtained in these arterial segments.

Renal duplex ultrasonography. All patients underwent bilateral RDUS in the noninvasive vascular laboratory, where velocities, pole-to-pole renal lengths, and RI values were recorded. These data were all obtained before any revascularization procedure. RDUS was performed in the usual protocol at our local noninvasive vascular laboratory, which is certified by the Intersocietal Commission for the Accreditation of Vascular Laboratories. Standard diagnostic equipment included Philips-ATL HDI 3000 ultrasound system (Bothell, Wash) with a 5.0-MHz to 2.0-MHz curved linear array probe or a 4.0-MHz to 2.0-MHz broadband phased array probe.

Statistical analysis. The primary study end point was the correlation between RI values determined by the invasive Doppler flow wire and noninvasive RDUS techniques using the Pearson correlation coefficient. Secondary end points included correlations of pole-to-pole renal length and renal arterial PSV and EDV. Also examined were time to perform invasive RI assessment, defined as the time when the Doppler wire was introduced into the renal artery to the time it was removed, and safety, including dissection, thrombosis, acute renal failure, and in-hospital dialysis.

Scatter plots of RI measurements, pole-to-pole renal length, PSV, and EDV determination were generated, and calculations were performed of the Pearson correlation, as well the Spearman correlation and the C-index coefficient with 95% confidence intervals (CI), by using the Fisher z transformation and bootstrapping. Neither the Pearson correlation nor the Spearman and C-index can detect scale or shift changes. Central tendency and scale of the two measurements were also compared by calculating means (using a paired t test) and comparing variances. Finally, we used linear mixed-effects models that regressed noninvasive and invasive velocity measurements that contained a random intercept for subjects. This was done to account for possible interdependence of measurements within subjects.

RESULTS

Between March 2005 and April 2006, 20 participants were enrolled and 35 renal arteries were studied. Table I summarizes the baseline patient characteristics. Average patient age was 67.2 ± 20 years, with a baseline serum creatinine of 1.31 ± 0.48 mg/dL, and calculated glomerular filtration rate of 57.6 ± 24.1 mL/min. RAS was

Table I. Patient baseline characteristics

Characteristic	*Value n = 20 (%)**
Renal arteries studied	35
Age	67.2 ± 20
Males	11 (55)
Baseline LVEF (%)	56.7 ± 18
Hypertension	16 (80)
Diabetes	9 (45)
PVD (not including RAS)	8 (40)
Antihypertensive agents (n)	2.7 ± 1.5
Serum creatinine (mg/dL)	1.31 ± 0.48
GFR† (mL/min)	57.6 ± 24
Average RAS diameter (%)	74.4 ± 14

LVEF, Left ventricular ejection fraction; *PVD,* peripheral vascular disease, *GFR,* glomerular filtration rate; *RAS,* renal artery stenosis.

*Data based on enrollment of 20 patients. N (%) listed for categoric variables; mean ± standard deviation listed for continuous variables where appropriate.

†Based upon modification of diet in renal disease equation.

identified in 17 patients (85%), with an average vessel stenosis severity of 74.4% ± 14.0%. All 20 attempted endovascular assessments of patients with RI were successful.

The study results are summarized in Table II. The mean right renal artery RI by invasive Doppler was 78 ± 20, with a corresponding right RI by RDUS of 78 ± 21. This yielded a right renal artery Pearson's coefficient value of 0.92. The mean left renal artery RI by invasive Doppler was 82 ± 21, with a corresponding left RI by RDUS of 81 ± 20, providing left renal system Pearson's coefficient value of 0.79. The overall *r* value comparing the two RI techniques was 0.86 (95% CI, 0.73 to 0.93). The results were then reanalyzed using linear mixed-effects models, as stated in our statistical methods. The results of these mixed effects models did not differ substantially from the one we report.

The mean right pole-to-pole renal length by angiography was 10.4 ± 3.1 cm, with a corresponding right pole-to-pole renal length by RDUS of 10.6 ± 2.7 cm ($r = 0.44$). The left pole-to-pole renal length by angiography was 10.9 ± 32.9 cm, with a corresponding left pole-to-pole renal length by RDUS 11.0 ± 2.8 cm ($r = 0.37$). The overall *r* value comparing the two techniques to assess pole-to-pole renal length was 0.43 (95% CI, 0.11 to 0.67).

PSV in the right renal arteries averaged 147 ± 110 cm/s by Doppler wire and 234 ± 130 cm/s by RDUS. In the left renal arteries, average PSV was 127 ± 102 cm/s by Doppler flow wire and 185 ± 110 cm/s by RDUS. The overall Pearson's coefficient value using a variance-stabilizing transformation was 0.66 (95% CI, 0.54 to 0.76). EDV in the right renal arteries average 18.5 ± 23.9 cm/s by Doppler wire and 28.5 ± 38.7 cm/s by RDUS. Average EDV in the left was 13.3 ± 12.3 cm/s by Doppler wire and 19.3 ± 18.9 cm/s by RDUS. The overall Pearson's coefficient value was 0.61 (95% CI, 0.48 to 0.72). The average time to perform an invasive RI assessment per renal artery was 10.9 ± 7.6 minutes. No major complications were noted during this study, including any episodes of vascular injury, thrombosis, acute renal failure, in-hospital dialysis, or death.

DISCUSSION

RAS is frequently identified by angiography before noninvasive physiologic assessment. This has become more common as a result of aggressive screening efforts among patients undergoing coronary and peripheral vascular procedures.[2,7] An emerging dilemma from this practice is the inability to adequately assess lesion significance at the time of angiography and identify those who would most likely benefit from revascularization. Although no clear consensus exists on the degree of renal artery narrowing that justifies revascularization, investigators generally define the minimal threshold for an angiographically significant arterial narrowing to be ≥50% luminal diameter reduction.[3,4] This is acknowledged as only an approximate guide to the hemodynamic effect of the stenosis.

Variables such a baseline mean blood pressure of >110 mm Hg and bilateral RAS have previously been used to predict improvement in blood pressure after RAR.[8,9] Neither has been prospectively validated. One common in-laboratory procedure is to measure translesional systolic gradients, with a value of >20 mm Hg considered significant and an indication for revascularization.[3] This technique has not been standardized nor validated with regard to clinical outcome after revascularization.[4]

The best-validated test that predicts clinical benefit after revascularization is noninvasive RDUS-derived RI, defined as [1− (EDV/PSV)] × 100. The RI is considered a useful measure of nephrosclerosis severity.

In a large single-center study, Radermacher et al[5] evaluated the utility of RI in predicting outcome (hypertension control, renal function, mortality) after elective revascularization in RAS patients. Of the 5950 patients screened, 138 underwent renal arterial revascularization by angioplasty or surgery. The 35 patients with an RI >80 experienced high rate (80%) of decrease in renal function, without significant improvement in hypertension control. In the 96 patients with an RI <80, 94% had improvement in blood pressure control, and only a small minority (3%) became dialysis-dependent.[5] Hence, the impact of revascularization on patients with high RI values appears to be marginal.

The RI remains to date the only physiologic characteristic that has been clinically validated as a predictor of outcomes.[4,6,10] Unfortunately, RI determination is typically performed in a separate noninvasive laboratory and thus cannot provide real-time data during endovascular procedures.

In RAIDER, we examined how well endovascular assessment of renal RI correlated with the traditional noninvasive technique. Noninvasive RIs were reported as an average of two to four measurements taken in the segmental artery and in the distal, mid, and proximal portions of the main renal artery. Invasive RI values similarly were reported as an average of measurements taken in similar arterial locations.

Our primary findings were robust. There was an excellent overall correlation between the two methods for RI acquisition ($r = 0.86$; 95% CI, 0.73 to 0.93; see Fig 2). The correlation for RI values assessed by the two techniques on each renal artery was also robust ($r = 0.92$ for the right, $r =$

Table II. Summary of study results*

Assessment	*Right*	*Left*	*Overall (95% CI)*
Renal resistive index			
Doppler flow wire	78 ± 20	82 ± 21	
Renal duplex ultrasound	78 ± 21	81 ± 20	
Assessment *r* value	0.92	0.79	0.86 (73-0.93)
Renal span (cm)			
Doppler flow wire	10.4 ± 3.1	10.9 ± 2.9	
Renal duplex ultrasound	10.6 ± 2.7	11.0 ± 2.8	
Assessment *r* value	0.44	0.37	0.43 (0.11-0.67)
Average renal PSV (cm/s)			
Doppler flow wire	147 ± 110	127 ± 102	
Renal duplex ultrasound	234 ± 130	185 ± 110	
Assessment *r* value			0.66 (0.54-0.76)
Average renal EDV (cm/s)			
Doppler flow wire	18.5 ± 23.9	13.3 ± 12.3	
Renal duplex ultrasound	28.5 ± 38.7	19.3 ± 18.9	
Assessment *r* value			0.61 (0.48-0.72)
Technical success (%)	100%	100%	

PSV, Peak systolic velocity; *EDV*, end-diastolic velocity.
*Data are presented as mean ± standard deviation.

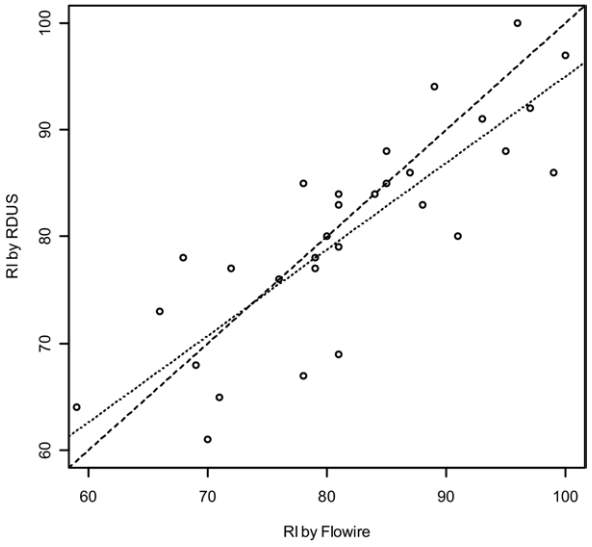

Fig 2. Scatter plot of renal index *(RI)* derived by catheter Doppler flow wire and renal duplex ultrasonography *(RDUS)*. A robust correlation is seen, with $r = 0.86$ (95% CI, 0.73 to 0.93).

0.79 for the left). Furthermore, the average time of <11 minutes per artery to perform the invasive RI assessment was reasonable; this included operator and staff learning curve for the device. We found the procedure to be safe, with no major immediate complications in our study.

These findings are in agreement with recent data from Slovut et al.[11] In their pilot study, they reported a moderate but significant correlation ($r = 0.63$) between noninvasive and endovascular measures of RI values in a cohort of 16 patients who were concomitantly undergoing renal flow reserve assessment.[11] Previous investigators have also reported similar use of endovascular flow wires to assess RI. Although they did not compare it directly with RDUS, they found the procedure to be relatively simple, rapid, and safe.[12,13]

Pole-to-pole renal length is another important part of the preintervention evaluation for RAS. A pole-to-pole renal length of <7 to 8 cm is considered evidence of significant renovascular disease and a predictor of poor response after stenting. We studied how well assessing pole-to-pole renal length by measuring contrast nephrograms during angiography correlated with traditional RDUS. Our findings suggested only a modest correlation ($r = 0.43$; 95% CI, 0.11 to 0.67). A possible explanation for this result involves how pole-to-pole renal length is measured. RDUS uses B-mode ultrasound imaging to measure size and is often technically difficult owing to obesity, patient movement, and excessive bowel gas. In our study, 10% of kidneys could not be measured for size by RDUS.

Conversely, neither of these factors typically interferes with pole-to-pole renal length assessment in the catheterization lab. The only instance where we were unable to size the kidney was when it did not appear on the imaging screen owing to diameter limitations of the image intensifier. This became less problematic during our recruitment with the addition of a modern endovascular suite (Philips Allura Xper FD 20) with a larger field of view. Overall, we were able to measure pole-to-pole renal length by angiography >97% of the time.

The present study also looked at the correlation between renal arterial PSV and EDV determined by both techniques and a moderate but significant correlation was found for both ($r = 0.66$ and $r = 0.61$, respectively). These findings were not as robust as the RI findings, however.

Possible explanations for this likely relate to how velocities are derived with these two techniques. RDUS relies on insonation of arteries at the point were the tightest lesions exist, optimally with an insonation angle of ≤60°.[14] The Doppler wire emits an ultrasound beam that diverges at

about 30°, with a sample volume 5 mm distal to the tip. Despite being more apt to send signals at optimal angles, this method may be affected by stenosis geometry, vessel tortuosity, and intravascular velocity profile. Moreover, no computer-assisted system is available that measures the angle between the transducer and flow vector. Velocities can also be affected by central hemodynamic conditions. Thus changes in circulatory conditions (eg, cardiac output, preload, afterload) potentially can change arterial velocities between times of RDUS and Doppler flow wire assessment.

All of these could account for the moderate correlation for PSV and EDV between the two methods. In fact, when we re-examined our invasive PSV data, no correlation was found with angiographic stenosis severity ($r = -0.03$). RI correlation, however, was strong in our study. This suggests the proportional difference between PSV and EDV are unchanged despite numerous factors that may affect how actual velocities are measured using the Doppler wire.

A number of potential study limitations should be mentioned:

First, endovascular Doppler assessment had not been commonly performed at our institution; hence, a period of time was required to become facile with this procedure.

Second, there was an average interval of about 50 days between the time of RDUS and the time of endovascular assessment. This time interval, as well as changes in disease state and hemodynamic conditions, may have confounded the data. However, based on our knowledge that RAS is a disease that progresses over years (not weeks),[15-17] we believe that any effect on our findings caused by the interval time would have been minimal.

Third, no efforts were made to withhold drugs that could have affected our investigation. Specifically, no systematic efforts were made to stop angiotensin-converting enzyme inhibitors or control for intraprocedural medications that could have affected renal arterial flow conditions.

Four, postprocedure creatinine levels were not routinely checked on all study patients. Thus, the safety profile in terms of distal embolization and late renal failure remains unknown.

CONCLUSION

RI values derived using an endovascular Doppler flow wire strongly correlate with RI values derived from traditional RDUS. Measurements of pole-to-pole renal length during angiography as well as assessing PSV also correlate with RDUS measurements, but only to a moderate extent. The procedure is safe, can be done in a reasonable time frame, and provides immediate feedback to the operator. Coupled with similar data in the existing literature, we believe an appropriate anatomic and physiologic assessment of renovascular disease can be performed during diagnostic angiography by using these techniques.

AUTHOR CONTRIBUTIONS

Conception and design: MD, RZ, AK, JR, CT
Analysis and interpretation: MD, TM, AK, CT
Data collection: MD, AK, JR, CT
Writing the article: MD, TM, AK, CT
Critical revision of the article: MD, TM, RZ, AK, JR, CT
Final approval of the article: MD, CT
Statistical analysis: MD, TM, CT
Obtained funding: MD, CT
Overall responsibility: MD, CT

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